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Macrophagic Myofasciitis: Evidence for Chronic Local and Systemic Immune Activation Associated with Persistence of Aluminum Hydroxide-Loaded Macrophages in Muscle

Romain K. Gherardi, Anne Plonquet, Chantal Andre, Liliane Intrator, Françoise Poron, Creteil, France, Michele Coquet, Bordeaux, France, François J. Authier, Creteil, France

OBJECTIVE: To define both local and systemic immunologic abnormalities observed in patients with macrophagic myofasciitis (MMF).

BACKGROUND: MMF is characterized by stereotyped accumulation of aluminum hydroxide-loaded macrophages, persisting for years at sites of i.m. injections of vaccines, typically detected in patients with diffuse steroid-responsive arthromyalgias and fatigue. 110 patients with MMF have been recognized so far in France and isolated cases have been recorded other countries. A concurrent autoimmune disease is observed in one third of patients.

DESIGN/METHODS: Muscle biopsies of 50 consecutive patients detected in Créteil and Bordeaux were reevaluated to examine the lymphoid component of the MMF lesion. Systemic investigations included screening of circulating auto-antibodies (n=20), determination of plasma concentrations of myalgias and fatigue-inducing cytokines (IL-1β, IL-1Ra, IL-6, TNFα and GM-CSF; n=17), and FACS analysis of PBMC subsets (n=7), all evaluations being performed before onset of steroid therapy.

RESULTS: A lymphoid component, ranging from lymphoplasmacytic infiltrates to organized tertiary lymphoid tissue, was constantly observed in MMF lesions (50/50). Intensity of lymphocytic infiltration was: +: 28/50 (56%); ++: 14/50 (28%); +++: 8/50 (16%). Most lymphocytes were CD3+, and usually CD8+, T-cells. Involvement of B-cells was assessed by lymphoid follicle formation (11/50, 22%) or presence of plasma cells (19/50, 38%). Eosinophils (10%) and mast cells (10%) were occasionally observed. HLA class I antigen was expressed by CD 68+ macrophages and adjacent muscle fibers. Circulating autoantibodies were detected in 50% of patients and mainly included antinuclear (6/20; 30%) and anti-phospholipid (4/20; 20%) autoantibodies. MMF patients had a significant increase of circulatory levels of IL-6 (p=0.016) and IL-1Ra (p=0.014). FACS analysis showed moderate (x2) but constant B-cell (CD19+) hyperlymphocytosis (7/7), mild increase of NK-cells (CD3-/CD16+/CD56+) (6/7), and normal CD3+, CD4+, CD8+, CD14+, CD28+, CD62L+ and CD45RA/CD45RO ratio.

CONCLUSIONS: Both local and systemic signs of protracted immune stimulation are constantly associated with MMF and could account for both systemic symptoms of affected patients and concurrent autoimmune disorders.

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Disclosure: Dr. Gherardi has nothing to disclose.

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High Incidence of Cardiac Arrhythmic Events in a Multicenter Myotonic Dystrophy Registry

William J. Groh, Miriam A. Lowe, Rahman Pourmand, Douglas P. Zipes, Indianapolis, IN

OBJECTIVE: To determine the incidence and predictive factors for cardiac arrhythmic disease in myotonic dystrophy (DM).

BACKGROUND: Patients (pts) with DM are at a high risk of cardiac arrhythmic disease including sudden death. Risk stratification and treatment for arrhythmias in DM is not clear.

DESIGN/METHODS: A registry of DM pts was established at 25 neurology clinics in the U.S. to evaluate cardiac abnormalities at study entry and to determine arrhythmic outcome during follow-up.

RESULTS: In 296 adult pts (148 male) with clinical and genetic diagnosis of DM, the age was 42±12 (18–78) years [mean±SD (range)], the age at disease onset was 23±13 (0–64) years, and the CTG repeat length (CTG) was 617±371 (54–1965). The severity of skeletal muscular involvement graded using a 5-point scale was 3.2±1.0 (1–5) with 18 pts (6.1%) having severe weakness. An inverse relationship was observed between age at disease onset and CTG (r=0.45, P<0.01). Both age and CTG were independently related to the severity of skeletal muscular involvement (r=0.47, P<0.01). The 12-lead electrocardiogram (ECG) in 296 pts and 24-hr ambulatory electrocardiogram (Holter) in 220 pts were obtained as measures of baseline cardiac conduction abnormalities and arrhythmias. In 191 (65%) pts the ECG was abnormal. The most common abnormality observed was impaired conduction with 77 pts (26%) showing a severe conduction abnormality consisting of a markedly prolonged PR interval >240 ms and/or a QRS duration >120 ms. Presence of cardiac conduction abnormalities and the severity of conduction abnormalities on the ECG correlated with older age, a more prolonged CTG, and male gender (P<0.01). The Holter monitoring was significantly abnormal in 24% including paroxysmal atrial fibrillation in 13 (6%), premature ventricular depolarizations > 10 per hour in 32 (15%), and nonsustained ventricular tachycardia in 11 (5%). At study entry, only 7 (2%) pts had received a pacemaker and only 3 (1%) had undergone a cardiac electrophysiologic study. Over a mean follow-up of 2.5±0.6 years (0.8–3.7), arrhythmic events have been reported in 17 (6%) including unexpected sudden death in 5 (2%), new onset symptomatic atrial fibrillation in 5 (2%), pacemaker implantation in 4 (1%), and unexplained syncope in 3 (1%). The ECG at study entry predicted arrhythmic events in that pts with events had both a more prolonged PR interval (214 vs. 192 ms, P=0.02) and QRS duration (114 vs. 103 ms, P=0.04).

CONCLUSIONS: Arrhythmic events are common in pts with DM and can be predicted by a simple ECG screening test. More aggressive cardiac evaluation and treatment may be warranted.

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Myopathology of Proximal Myotonic Myopathy (PROMM)

Guillaume Bassez, Créteil, France, Pascal Laforêt, Andrés Rouche, Thierry Maisonobe, Paris, France, Romain K. Gherardi, Crétail, France, Michel Fardeau, Bruno Eymard, Paris, France

OBJECTIVE: To report myopathological features of proximal myotonic myopathy (PROMM).

BACKGROUND: PROMM belongs to the group of dominantly inherited multisystem myotonic disorders. PROMM phenotype shares numerous clinical features with myotonic dystrophy (DM1) in the absence of CTG repeat expansion at the DM locus. However, distinct clinical features exist including muscle pain, preferentially proximal weakness in lower limbs and mild inconstantly detected clinical myotonia. In contrast to suggestive histopathological abnormalities of DM1, muscle biopsy findings in PROMM have been described as relatively non-specific or compatible with neuropathic changes, including abnormal variability in fiber diameter, angular fibers, increased internal nuclei and frequent nuclear clumps.

DESIGN/METHODS: Muscle biopsies from 11 patients fulfilling diagnosis criteria for PROMM were reevaluated and compared to biopsies from patients with DM1 confirmed by abnormal CTG expansion (6), or with motor neuron disease (6). The evaluation focussed on angular fibers, fiber type grouping, central nuclei, nuclear clumps and ring fibers. Histogram of both fiber types diameter was evaluated in the deltoid muscle from six PROMM patients and six age-matched DM1 patients.

RESULTS: Type I fiber predominance, high number of central nuclei and nuclear clumps were observed in muscle biopsies from both groups PROMM and DM1. In PROMM, size histogram showed no selective type I fiber atrophy (p<0.05), but rather a frequent preferential type II fiber atrophy. Ring fibers were rare. Despite occasional angular atrophic fibers and abundant nuclear clumps, neuropathic fiber type grouping was not detected in PROMM.

CONCLUSIONS: In contrast to close clinical similarities between PROMM and DM1, muscle biopsy analysis suggests dis-

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